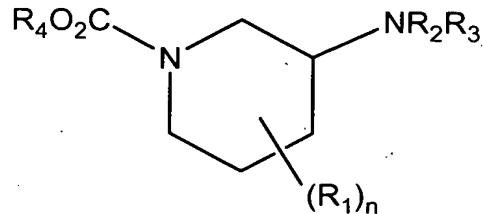


What is claimed is:

1. A method of making a compound of formula (Ia)

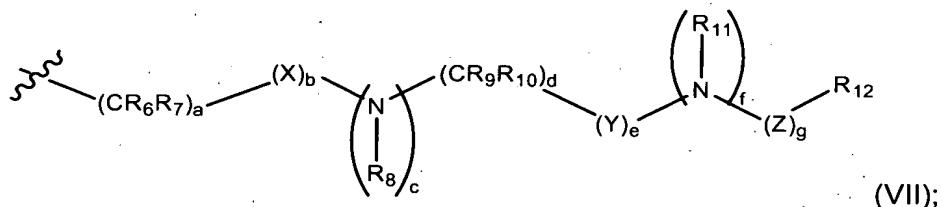


5

wherein R<sub>1</sub> is carboxy, cyano, deuterium, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>6</sub>)acyl, (C<sub>1</sub>-C<sub>6</sub>)alkylamino, amino(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy-CO-NH, (C<sub>1</sub>-C<sub>6</sub>)alkylamino-CO-, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>2</sub>-C<sub>6</sub>)alkynyl, (C<sub>1</sub>-C<sub>6</sub>)alkylamino, amino(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)acyloxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, nitro, cyano(C<sub>1</sub>-C<sub>6</sub>)alkyl, nitro(C<sub>1</sub>-C<sub>6</sub>)alkyl, trifluoromethyl, trifluoromethyl(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)acylamino, (C<sub>1</sub>-C<sub>6</sub>)acylamino(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>1</sub>-C<sub>6</sub>)acylamino, amino(C<sub>1</sub>-C<sub>6</sub>)acyl, amino(C<sub>1</sub>-C<sub>6</sub>)acyl(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkylamino(C<sub>1</sub>-C<sub>6</sub>)acyl, ((C<sub>1</sub>-C<sub>6</sub>)alkyl)<sub>2</sub>amino(C<sub>1</sub>-C<sub>6</sub>)acyl, R<sub>15</sub>R<sub>16</sub>N-CO-O-, R<sub>15</sub>R<sub>16</sub>N-CO-(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkyl-S(O)<sub>m</sub>, R<sub>15</sub>R<sub>16</sub>NS(O)<sub>m</sub>, R<sub>15</sub>R<sub>16</sub>NS(O)<sub>m</sub>(C<sub>1</sub>-C<sub>6</sub>)alkyl, R<sub>15</sub>S(O)<sub>m</sub>R<sub>16</sub>N, R<sub>15</sub>S(O)<sub>m</sub>R<sub>16</sub>N(C<sub>1</sub>-C<sub>6</sub>)alkyl or a group of the formula (VII)

10

15



R<sub>2</sub> is hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkylsulfonyl, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, or (C<sub>2</sub>-C<sub>6</sub>)alkynyl wherein the alkyl, alkenyl and alkynyl groups are optionally substituted by deuterium, hydroxy, trifluoromethyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, (C<sub>1</sub>-C<sub>6</sub>)acyloxy, (C<sub>1</sub>-C<sub>6</sub>)alkylamino, ((C<sub>1</sub>-C<sub>6</sub>)alkyl)<sub>2</sub>amino, cyano, nitro, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>2</sub>-C<sub>6</sub>)alkynyl or (C<sub>1</sub>-C<sub>6</sub>)acylamino; or R<sub>2</sub> is (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl wherein the cycloalkyl group is optionally substituted by deuterium, hydroxy, trifluoromethyl, (C<sub>1</sub>-C<sub>6</sub>)acyloxy, (C<sub>1</sub>-C<sub>6</sub>)acylamino, (C<sub>1</sub>-C<sub>6</sub>)alkylamino, ((C<sub>1</sub>-C<sub>6</sub>)alkyl)<sub>2</sub>amino, cyano, cyano(C<sub>1</sub>-C<sub>6</sub>)alkyl, trifluoromethyl(C<sub>1</sub>-C<sub>6</sub>)alkyl, nitro, nitro(C<sub>1</sub>-C<sub>6</sub>)alkyl or (C<sub>1</sub>-C<sub>6</sub>)acylamino;

R<sub>3</sub> is hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, or (C<sub>2</sub>-C<sub>6</sub>)alkynyl wherein the alkyl, alkenyl and alkynyl groups are optionally substituted

by deuterium, hydroxy, halogen, trifluoromethyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, (C<sub>1</sub>-C<sub>6</sub>)acyloxy, (C<sub>1</sub>-C<sub>6</sub>)alkylamino, (C<sub>1</sub>-C<sub>6</sub>)acylamino, ((C<sub>1</sub>-C<sub>6</sub>)alkyl)<sub>2</sub>amino, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>2</sub>-C<sub>6</sub>)alkynyl, cyano, cyano(C<sub>1</sub>-C<sub>6</sub>)alkyl, trifluoromethyl(C<sub>1</sub>-C<sub>6</sub>)alkyl, nitro, or nitro(C<sub>1</sub>-C<sub>6</sub>)alkyl;

5 R<sub>4</sub> is (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, or (C<sub>2</sub>-C<sub>6</sub>)alkynyl wherein the alkyl, alkenyl and alkynyl groups are optionally substituted by deuterium, hydroxy, halogen, amino, trifluoromethyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, (C<sub>1</sub>-C<sub>6</sub>)acyloxy, (C<sub>1</sub>-C<sub>6</sub>)alkylamino, (C<sub>1</sub>-C<sub>6</sub>)acylamino, ((C<sub>1</sub>-C<sub>6</sub>)alkyl)<sub>2</sub>amino, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>2</sub>-C<sub>6</sub>)alkynyl, cyano, cyano(C<sub>1</sub>-C<sub>6</sub>)alkyl, trifluoromethyl(C<sub>1</sub>-C<sub>6</sub>)alkyl, nitro, or nitro(C<sub>1</sub>-C<sub>6</sub>)alkyl;

10 R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub>, R<sub>9</sub>, R<sub>10</sub> and R<sub>11</sub> are each independently hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted by deuterium, hydroxy, trifluoromethyl, (C<sub>1</sub>-C<sub>6</sub>)acyloxy, (C<sub>1</sub>-C<sub>6</sub>)acylamino, (C<sub>1</sub>-C<sub>6</sub>)alkylamino, ((C<sub>1</sub>-C<sub>6</sub>)alkyl)<sub>2</sub>amino, cyano, cyano(C<sub>1</sub>-C<sub>6</sub>)alkyl, trifluoromethyl(C<sub>1</sub>-C<sub>6</sub>)alkyl, nitro, nitro(C<sub>1</sub>-C<sub>6</sub>)alkyl or (C<sub>1</sub>-C<sub>6</sub>)acylamino; R<sub>12</sub> is

15 carboxy, cyano, amino, oxo, deuterium, hydroxy, trifluoromethyl, (C<sub>1</sub>-C<sub>6</sub>)alkyl, trifluoromethyl(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>6</sub>)acyl, (C<sub>1</sub>-C<sub>6</sub>)alkylamino, ((C<sub>1</sub>-C<sub>6</sub>)alkyl)<sub>2</sub>amino, amino(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy-CO-NH, (C<sub>1</sub>-C<sub>6</sub>)alkylamino-CO-, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>2</sub>-C<sub>6</sub>)alkynyl, (C<sub>1</sub>-C<sub>6</sub>)alkylamino, hydroxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)acyloxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, nitro, cyano(C<sub>1</sub>-C<sub>6</sub>)alkyl, nitro(C<sub>1</sub>-C<sub>6</sub>)alkyl, trifluoromethyl, trifluoromethyl(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)acylamino, (C<sub>1</sub>-C<sub>6</sub>)acylamino(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>1</sub>-C<sub>6</sub>)acylamino, amino(C<sub>1</sub>-C<sub>6</sub>)acyl, amino(C<sub>1</sub>-C<sub>6</sub>)acyl(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkylamino(C<sub>1</sub>-C<sub>6</sub>)acyl, ((C<sub>1</sub>-C<sub>6</sub>)alkyl)<sub>2</sub>amino(C<sub>1</sub>-C<sub>6</sub>)acyl, R<sub>15</sub>R<sub>16</sub>N-CO-O-, R<sub>15</sub>R<sub>16</sub>N-CO-(C<sub>1</sub>-C<sub>6</sub>)alkyl, R<sub>15</sub>C(O)NH, R<sub>15</sub>OC(O)NH, R<sub>15</sub>NHC(O)NH, (C<sub>1</sub>-C<sub>6</sub>)alkyl-S(O)<sub>m</sub>, (C<sub>1</sub>-C<sub>6</sub>)alkyl-S(O)<sub>m</sub>-(C<sub>1</sub>-C<sub>6</sub>)alkyl, R<sub>15</sub>R<sub>16</sub>NS(O)<sub>m</sub>,

25 R<sub>15</sub>R<sub>16</sub>NS(O)<sub>m</sub>(C<sub>1</sub>-C<sub>6</sub>)alkyl, R<sub>15</sub>S(O)<sub>m</sub>R<sub>16</sub>N, or R<sub>15</sub>S(O)<sub>m</sub>R<sub>16</sub>N(C<sub>1</sub>-C<sub>6</sub>)alkyl;

R<sub>15</sub> and R<sub>16</sub> are each independently hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl;

X is S(O)<sub>p</sub>, oxygen, carbonyl or -C(=N-cyano)-;

Y is S(O)<sub>p</sub> or carbonyl;

Z is S(O)<sub>p</sub>, carbonyl, C(O)O-, or C(O)NR-;

30 a is 0, 1, 2, 3 or 4;

b, c, e, f and g are each independently 0 or 1;

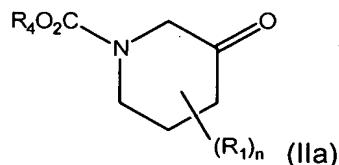
d is 0, 1, 2, or 3;

m is 0, 1 or 2;

n is 1, 2, 3, or 4;

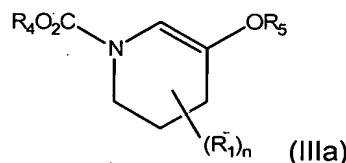
p is 0, 1 or 2; and

wherein the method comprises reacting  $\text{NHR}_2\text{R}_3$ ,  $\text{N}(\text{CH}_3)\text{R}_2\text{H}$ , or  $\text{N}(\text{CH}_2\text{CH}_3)\text{R}_2\text{H}$  with a compound of formula (IIa)



5 and reducing the compound so formed with a reducing agent.

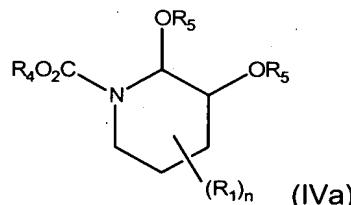
2. The method of claim 1, wherein the method further comprises formation of the compound of the formula (IIa) by reacting a compound having the formula  $\text{R}_4\text{OH}$ , water, or  $\text{R}_4\text{NH}_2$  and a compound of the formula (IIIa)



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wherein  $\text{R}_5$  is  $\text{CO}(\text{C}_1\text{-C}_6)\text{alkyl}$ .

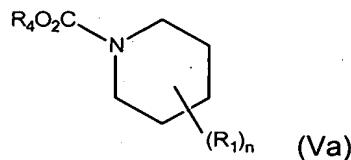
3. The method of claim 2, wherein the method further comprises formation of the compound of the formula (IIIa) by heating a compound having the formula (IVa)



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with a compound having the formula  $(\text{C}_1\text{-C}_6)\text{alkyl}-(\text{C=O})-\text{O}-(\text{C=O})-(\text{C}_1\text{-C}_6)\text{alkyl}$ .

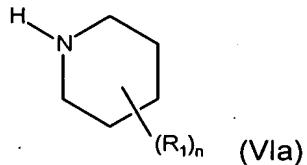
4. The method of claim 3, wherein the method further comprises formation of the compound of the formula (IVa) by oxidizing a compound having the formula (Va)



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under oxidizing conditions.

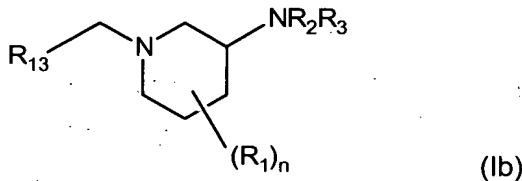
5. The method of claim 4, wherein the method further comprises formation of the compound of the formula (Va) by reacting a compound having the formula  $WCO_2R_4$  and a compound having the formula (ViA)



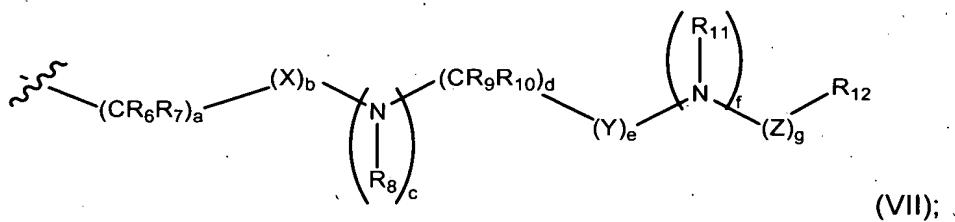
5 wherein W is halogen.

6. The method of claim 4, wherein the oxidizing conditions are an electrochemical oxidation.

10 7. A method of making a compound having the formula (Ib)



wherein  $R_1$  is carboxy, amino, deuterium, hydroxy, ( $C_1-C_6$ )alkyl, ( $C_1-C_6$ )alkoxy, ( $C_1-C_6$ )alkylamino, amino( $C_1-C_6$ )alkyl, ( $C_2-C_6$ )alkenyl, ( $C_2-C_6$ )alkynyl, ( $C_1-C_6$ )alkylamino, amino( $C_1-C_6$ )alkyl, hydroxy( $C_1-C_6$ )alkyl, ( $C_1-C_6$ )alkoxy( $C_1-C_6$ )alkyl, nitro, nitro( $C_1-C_6$ )alkyl, trifluoromethyl, trifluoromethyl( $C_1-C_6$ )alkyl, ( $C_1-C_6$ )alkyl-S(O)<sub>m</sub>,  $R_{15}R_{16}NS(O)_m$ ,  $R_{15}R_{16}NS(O)_m$  ( $C_1-C_6$ )alkyl,  $R_{15}S(O)_mR_{16}N$ ,  $R_{15}S(O)_mR_{16}N(C_1-C_6)$ alkyl or a group of the formula (VII)



20  $R_2$  is hydrogen, ( $C_1-C_6$ )alkyl, ( $C_1-C_6$ )alkylsulfonyl, ( $C_2-C_6$ )alkenyl, or ( $C_2-C_6$ )alkynyl wherein the alkyl, alkenyl and alkynyl groups are optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, ( $C_1-C_4$ )alkoxy, ( $C_1-C_6$ )alkylamino, (( $C_1-C_6$ )alkyl)<sub>2</sub>amino, nitro, ( $C_2-C_6$ )alkenyl, or ( $C_2-C_6$ )alkynyl; or  $R_2$  is ( $C_3-C_{10}$ )cycloalkyl wherein the cycloalkyl group is optionally substituted by deuterium,

hydroxy, amino, trifluoromethyl, ( $C_1$ - $C_6$ )alkylamino, (( $C_1$ - $C_6$ )alkyl)<sub>2</sub>amino, trifluoromethyl( $C_1$ - $C_6$ )alkyl, nitro, or nitro( $C_1$ - $C_6$ )alkyl;

R<sub>3</sub> is hydrogen, ( $C_1$ - $C_6$ )alkyl, ( $C_3$ - $C_{10}$ )cycloalkyl, ( $C_2$ - $C_6$ )alkenyl, or ( $C_2$ - $C_6$ )alkynyl wherein the alkyl, alkenyl and alkynyl groups are optionally substituted  
5 by deuterium, hydroxy, amino, trifluoromethyl, ( $C_1$ - $C_4$ )alkoxy, ( $C_1$ - $C_6$ )alkylamino, (( $C_1$ - $C_6$ )alkyl)<sub>2</sub>amino, ( $C_2$ - $C_6$ )alkenyl, ( $C_2$ - $C_6$ )alkynyl, trifluoromethyl( $C_1$ - $C_6$ )alkyl, nitro, or nitro( $C_1$ - $C_6$ )alkyl;

R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub>, R<sub>9</sub>, R<sub>10</sub> and R<sub>11</sub> are each independently hydrogen or ( $C_1$ - $C_6$ )alkyl optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, ( $C_1$ -

10  $C_6$ )alkylamino, (( $C_1$ - $C_6$ )alkyl)<sub>2</sub>amino, trifluoromethyl( $C_1$ - $C_6$ )alkyl, nitro, or nitro( $C_1$ - $C_6$ )alkyl; R<sub>12</sub> is carboxy, amino, deuterium, hydroxy, trifluoromethyl, ( $C_1$ - $C_6$ )alkyl, trifluoromethyl( $C_1$ - $C_6$ )alkyl, ( $C_1$ - $C_6$ )alkoxy, ( $C_1$ - $C_6$ )alkylamino, (( $C_1$ - $C_6$ )alkyl)<sub>2</sub> amino, amino( $C_1$ - $C_6$ )alkyl, ( $C_2$ - $C_6$ )alkenyl, ( $C_2$ - $C_6$ )alkynyl, ( $C_1$ - $C_6$ )alkylamino, hydroxy( $C_1$ - $C_6$ )alkyl, ( $C_1$ - $C_6$ )alkoxy( $C_1$ - $C_6$ )alkyl, nitro, nitro( $C_1$ - $C_6$ )alkyl, trifluoromethyl,  
15 trifluoromethyl( $C_1$ - $C_6$ )alkyl, ( $C_1$ - $C_6$ )alkyl-S(O)<sub>m</sub>, ( $C_1$ - $C_6$ )alkyl-S(O)<sub>m</sub>-( $C_1$ - $C_6$ )alkyl, R<sub>15</sub>R<sub>16</sub>NS(O)<sub>m</sub>, R<sub>15</sub>R<sub>16</sub>NS(O)<sub>m</sub>( $C_1$ - $C_6$ )alkyl, or R<sub>15</sub>S(O)<sub>m</sub>R<sub>16</sub>N, or R<sub>15</sub>S(O)<sub>m</sub>R<sub>16</sub>N( $C_1$ - $C_6$ )alkyl;

R<sub>13</sub> is ( $C_2$ - $C_6$ )alkenyl, ( $C_2$ - $C_6$ )alkynyl, ( $C_6$ - $C_{10}$ )aryl, ( $C_1$ - $C_6$ )carboalkoxy, ( $C_5$ -  
20  $C_9$ )heteroaryl, ( $C_6$ - $C_{10}$ )aryl( $C_1$ - $C_6$ )alkyl, or ( $C_5$ - $C_9$ )heteroaryl( $C_1$ - $C_6$ )alkyl wherein the R<sub>13</sub> group is optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, ( $C_1$ - $C_6$ )alkyl, ( $C_1$ - $C_4$ )alkoxy, ( $C_1$ - $C_6$ )alkylamino, (( $C_1$ - $C_6$ )alkyl)<sub>2</sub>amino, ( $C_2$ - $C_6$ )alkenyl, ( $C_2$ - $C_6$ )alkynyl, trifluoromethyl( $C_1$ - $C_6$ )alkyl, nitro, or nitro( $C_1$ - $C_6$ )alkyl;

R<sub>15</sub> and R<sub>16</sub> are each independently hydrogen or ( $C_1$ - $C_6$ )alkyl;

X is S(O)<sub>p</sub>;

Y is S(O)<sub>p</sub>;

Z is S(O)<sub>p</sub>;

a is 0, 1, 2, 3 or 4;

b, c, e, f and g are each independently 0 or 1;

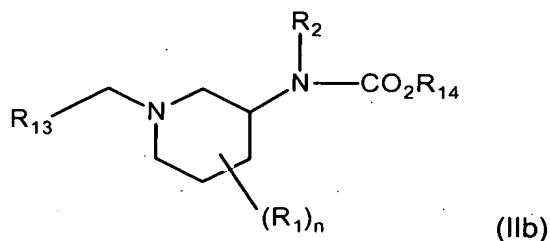
d is 0, 1, 2, or 3;

30 m is 0, 1 or 2;

n is 1, 2, 3, or 4;

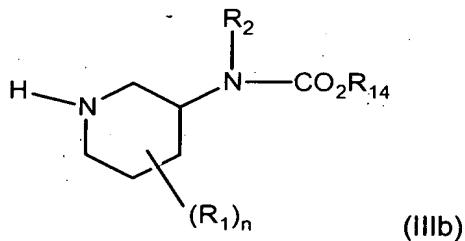
p is 0, 1 or 2; and

wherein the method comprises reducing a compound of formula (IIb)



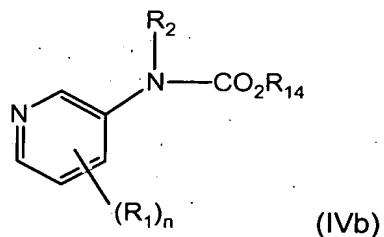
with a reducing agent, wherein R<sub>14</sub> is (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, or (C<sub>2</sub>-C<sub>6</sub>)alkynyl wherein the alkyl, alkenyl and alkynyl groups are optionally substituted by deuterium, hydroxy, halogen, amino, trifluoromethyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, (C<sub>1</sub>-C<sub>6</sub>)alkylamino, ((C<sub>1</sub>-C<sub>6</sub>)alkyl)<sub>2</sub>amino, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>2</sub>-C<sub>6</sub>)alkynyl, trifluoromethyl(C<sub>1</sub>-C<sub>6</sub>)alkyl, nitro, or nitro(C<sub>1</sub>-C<sub>6</sub>)alkyl.

8. The method of claim 7, wherein the method further comprises formation of the compound of the formula (IIb) by reacting a compound having the formula (IIIb)



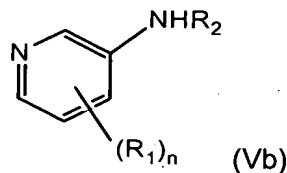
10 with an aldehyde of formula R<sub>13</sub>-(C=O)-H and reducing the compound so formed with a reducing agent.

9. The method of claim 8, wherein the method further comprises formation of the compound of the formula (IIIb) by hydrogenating a compound having the formula (IVb)



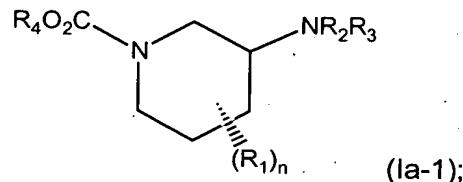
in the presence of a catalyst.

20 10. The method of claim 9, wherein the method further comprises formation of the compound of the formula (IVb) by reacting a compound having the formula (Vb)



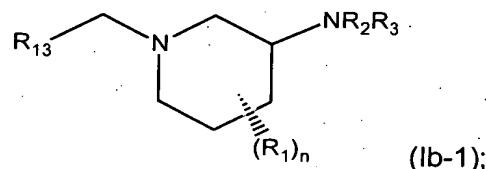
with  $(R_{14}\text{-O-(C=O)})_2\text{O}$  or  $R_{14}\text{-O-(C=O)-X}$  wherein X is halo.

11. The method of claim 1, wherein the compound of formula (Ia) has the relative  
5 stereochemistry of formula (Ia-1)



$R_1$  is  $(C_1\text{-}C_6)\text{alkyl}$ ; n is one;  $R_2$  and  $R_3$  are each hydrogen or  $(C_1\text{-}C_6)\text{alkyl}$ ; and  $R_4$  is  $(C_1\text{-}C_6)\text{alkyl}$ .

10 12. The method of claim 7, wherein the compound of formula (Ib) has the relative  
stereochemistry of formula (Ib-1)



$R_1$  is  $(C_1\text{-}C_6)\text{alkyl}$ ; n is one;  $R_2$  and  $R_3$  are each hydrogen or  $(C_1\text{-}C_6)\text{alkyl}$ ; and  $R_{13}$  is  $(C_6\text{-}C_{10})\text{aryl}$ .

15

13. The method of claim 1, wherein the reducing agent is a borohydride.

14. The method of claim 7, wherein the reducing agent is lithium aluminum hydride.

20

15. The method of claim 9, wherein the catalyst is Rh/alumina or Rh/C.